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Atty. Dkt. No. 036481-0127

*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*
*BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES*

Applicant: O'CONNOR *et al.*

Title: Hydrogel Particle Formulation

Appl. No.: 09/922,218

Filing Date: 8/3/2001

Examiner: Rachel M. Bennett

Art Unit: 1615

## BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants appeal from the final Office Action, dated January 26, 2004, which rejected claims 64-71 and 81-87. A Notice of Appeal was filed in this case on April 26, 2004 together with a check in the amount of $330.00 covering the section 1.17(b) appeal fee. Under the provisions of 37 C.F.R. § 1.192, this Appeal Brief is being filed in triplicate together with a check in the amount of $330.00 covering the Rule 17(c) appeal fee. If this fee is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

## REAL PARTY IN INTEREST

The real party in interest of the above-identified application is PowderMed Ltd., a limited liability company based in Oxford, United Kingdom. PowderMed is the assignee of the entire interest in this application.

## RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

## STATUS OF CLAIMS

Claims 1-38 are cancelled. Claims 39-63 and claims 72-80 are withdrawn from consideration. Claims 64-71 and 81-87 stand finally rejected under De Ponti *et al.* (GB 2245831) and are presently appealed. A full listing of the pending claims is included in Appendix A.

## STATUS OF AMENDMENTS

No amendments after final have been submitted by the applicants. The claims as of the Final Rejection date are the claims presented for appeal.

## SUMMARY OF INVENTION

The claimed invention relates to a method of making a powdered pharmaceutical composition. *See* the 09/922,218 application (the "'218 application") or the corresponding United States Publication No. 2002/0061336 (the "'336 publication"). The pharmaceutical composition includes one or more pharmacologically active agents incorporated into a hydrogel particle. A pharmacologically active agent may be any compound or composition of matter, which, when administered to an organism (human or animal subject), induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. *See* '218 application, p. 14, ll. 20-25 and '336 publication, paragraph [0065]. The term therefore encompasses those compounds or chemicals traditionally regarded as drugs, biopharmaceuticals (including molecules such as peptides, proteins, nucleic acids), vaccines, and gene therapies (*e.g.*, gene constructs). Applicants consider many pharmacologically active agents to be within the scope of the invention, for example, the agents described in the

'218 application, p. 14, ll. 25-30 and p. 20, ll. 1-4 and the '336 publication, paragraphs [0066] to [0075]. The invention further entails a composition where the active agent is present in the powdered pharmaceutical composition in an amount ranging from about 0.1 to 85 wt% of the composition.

The hydrogel particles according to the present invention can be made from a number of naturally-occurring or synthetically prepared or modified materials. *See* '218 application, p. 9, l. 15-30 and p.10, ll. 1-5 and '336 publication, paragraph [0039]. Generally, a hydrogel is a material comprising a macromolecular three-dimensional network that allows it to swell in the presence of water and to shrink in the absence of or reduction of the amount of water, but does not allow it to substantially dissolve in water. *Id.* The swelling may be due to the presence of hydrophilic functional groups that are attached to or dispersed within the macromolecular network. *Id.* The aqueous insolubility of these hydrogels, on the other hand, is primarily a result of cross-links that are formed between adjacent macromolecules. *Id.* The cross-links may be formed by chemical bonds, for example, covalent bonds, or by physical interactions, such as Van Der Waal forces, hydrogen-bonding, and ionic forces. *Id.* Naturally occurring hydrogels useful in this invention include various polysaccharides available from natural sources such as plants, algae, fungi, yeasts, marine invertebrates and arthropods. *See* '218 application, p. 12, l. 30 and p. 13, ll. 1-5 and '336 publication, paragraph [0059]. Examples of hydrogels include agarose, dextran, cellulose, chitin, starch, polyvinylpyrrolidone or polyvinyl alcohol. *See* claim 68.

Synthetically prepared hydrogels can be pre-formed by polymerizing a monomeric material to form a backbone and cross-linking the backbone with a cross-linking agent. *See* '218 application, p. 10, ll. 6-25 and '336 publication, paragraph [0040]. Alternatively, some

synthetic hydrogels are made by free radical polymerization of hydrophilic vinyl monomers. *See* '218 application, p. 10, ll. 26-30 and p. 11, ll. 1-4 and '336 publication, paragraph [0041].

The claimed process of making a powdered pharmaceutical composition includes:

(a) providing a mixture of pre-formed hydrogel particles;

(b) contacting the hydrogel particles with an aqueous composition containing at least one pharmacologically active agent for a period sufficient to allow the agent to associate with the hydrogel particles and be incorporated therewith;

(c) separating the hydrogel particles from the aqueous composition in at least a partial drying step to obtain primary loaded hydrogel particles having the active agent incorporated therewith;

(d) contacting the primary loaded hydrogel particles with an aqueous composition containing said pharmacologically active agent for a period sufficient to allow further agent to associate with the hydrogel particles and be incorporated therewith;

(e) separating the hydrogel particles formed in step (d) from the aqueous composition in at least a partial drying step to obtain secondary loaded hydrogel particles having the active agent incorporated therewith; and

(f) drying the secondary loaded hydrogel particles to obtain a powdered pharmaceutical composition. *See* claim 64.

Additionally, prior to the final drying step, the secondary loaded hydrogel particles formed in step (e) can be contacted at least one further time with an aqueous composition containing the pharmacologically active agent(s) for another period sufficient to allow still further agent(s) to associate with the hydrogel particles and be incorporated therewith. As

shown in Figures 2 and 3 of the present specification, when the number of loading periods increases, the percent of the insulin loaded also increases.

In a further embodiment of the invention, the hydrogel particles provided are contacted with the aqueous composition while in a dry state. Alternatively, they may be contacted with the aqueous composition while in a wet, prehydrated state. Finally, the powdered pharmaceutical composition may be formed by using a freeze-drying step or by using a spray-drying step.

The powdered pharmaceutical composition may be useful for transdermal delivery of one or more pharmacologically active agents. *See* '218 application, p. 3, ll. 11-17 and '336 publication, paragraph [0007]. In other words, the composition can be administered to a subject through the surface of the subject's skin or through one or more of the subject's mucosal sites. The ability to deliver pharmacologically active agents through skin surfaces provides distinct advantages over oral or parenteral delivery techniques. In particular, transdermal delivery provides a safe, convenient, and noninvasive alternative to traditional administration systems. It avoids the problems associated with oral delivery, such as variable rates of absorption and metabolism, gastrointestinal irritation, and bitter or unpleasant drug tastes. *See* ' 218 application, p. 1, ll. 9-17 and '336 publication, paragraph [0002]. In addition, it avoids the problems associated with parenteral delivery, for example, needle pain, the risk of introducing infection to treated individuals, the risk of infection of health care workers caused by accidental needle-sticks, and the disposal of used needles. *Id.*

Once the powdered pharmaceutical composition is administered into the skin or mucosal site, the agent is released to the subject's system by one of several mechanisms. Once the hydrogel is in an aqueous environment, the macromolecular network will expand,

thus releasing the agent and/or, if the macromolecular network is biodegradable, it will erode and release the compound. *See* '218 application, p. 10, ll. 6-25 and '336 publication, paragraph [0040]. The agent can enter particular cells or it can enter the subject's bloodstream and perform its intended diagnostic, therapeutic, or preventative functions.

## ISSUES

The first issue on appeal is whether the Examiner properly established a *prima facie* case of obviousness of claims 64-71 and 81-87 under 35 U.S.C. § 103(a).

The second issue on appeal is whether the Examiner properly concluded that the claimed invention was obvious under 35 U.S.C. § 103(a).

## GROUPING OF CLAIMS

There are at least two distinct claim groups present for appeal. Group I includes claim 64-71 and is directed to a method for making a powdered pharmaceutical composition by twice contacting hydrogel particles with an aqueous composition containing at least one pharmacologically active agent for a period sufficient to allow the agent to associate with the hydrogel particles and by twice separating the hydrogel particles from the aqueous composition in at least a partial drying step and then drying the particles to obtain a powdered pharmaceutical composition. Group II includes claim 81-87 and is directed to a method for making a powdered pharmaceutical composition by contacting hydrogel particles at least twice with an aqueous composition containing at least one pharmacologically active agent for a period sufficient to allow the agent to associate with the hydrogel particles and by at least twice separating the hydrogel particles from the aqueous composition in at least a partial drying step and then drying the particles to obtain a powdered pharmaceutical composition.

The claims in each group do not stand or fall together as discussed in the Argument section below.

## ARGUMENT

### Claims 64-71 and 81-87 Would Not Have Been Obvious Over De Ponti

Section 103(a) of Title 35 of the United States Code states that a patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." According to the Manual of Patent Examining Procedure ("MPEP"), an Examiner bears the initial burden of establishing a *prima facie* case of obviousness. If the Examiner produces a *prima facie* case, the burden then shifts to the applicants who may submit evidence of nonobviousness.

In order to establish a *prima facie* case of obviousness, three basic requirements must be met. MPEP § 2142 (8th ed. 2001). First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the references' teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

When assessing these issues, (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole and must suggest the desirability of making the combination; (c) the references must be viewed without the benefit of impermissible hindsight; and (d) a reasonable expectation of success is the standard with which obviousness

is determined. *See Hodosh v. Block Drug Co., Inc.*, 229 U.S.P.Q. 182, 187 n. 5 (Fed. Cir. 1986).

To assist in the assessment of obviousness with respect to a claimed invention, the Supreme Court has instructed that certain factual inquiries are critical. *See Graham v. John Deere Co.*, 383 U.S. 1 (1966). The factual inquiries include: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) secondary considerations of nonobviousness. *Id.* at 17-18. These facts must be considered when determining whether a *prima facie* case of obviousness has been established. *Id.*

**I. Claim Construction**

The first step in any obviousness analysis is, of course, to construe the language of the claims. *See Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1362 (Fed. Cir. 1998) ("The first step in any invalidity or infringement analysis is claim construction."). During examination, "claims ... are to be given their broadest reasonable interpretation consistent with the specification, and ... claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Bond*, 910 F.2d 831, 833 (Fed. Cir. 1990); *accord In re Bass*, 314 F.3d 575, 577 (Fed. Cir. 2002) ("[T]he PTO must apply the broadest reasonable meaning to the claim language, taking into account any definitions presented in the specification.").

Independent claim 64 is recited in Appendix A and is directed to a method for making a powdered pharmaceutical composition. The Examiner in this case has not disputed the scope of claim 64 or indicated that the terms should take on a meaning different from the ordinary and customary meaning of the terms read in light of the specification. Accordingly,

applicants submit that the claim terms should be construed consistently with their ordinary meaning and with the specification.

Independent claim 81 is also recited in Appendix A and is directed to a method for making a powdered pharmaceutical composition. Independent claim 81 differs from claim 64 by the recitation of at least one further contact with an aqueous composition containing said pharmacologically active agent and at least one further separation in at least a partial drying step. These elements indicate that the contact/drying process is reiterative and the hydrogel particles may be contacted with the aqueous composition and then partially dried several times before the final drying step. Again, applicants submit that the claim terms should be construed consistently with their ordinary meaning and with the specification.

**II. Scope of the Prior Art**

The prior art reference asserted by the Examiner, De Ponti *et al.* (GB 2,245,831 A) ("De Ponti"), was filed on July 4, 1991 and was published on January 15, 1992. It generally describes, as the Examiner asserts, a formulation for treating burns or wounds comprising a powder of water-insoluble and water-swellable polysaccharide microspheres loaded with a heparin-binding growth factor. The powder has gel-forming abilities and is typically a lyophilized powder. *See* De Ponti, page 4, ll. 2-4. Moreover, the microspheres are normally biodegradable and can be made of cellulose, a cellulose derivative, starch, a starch derivative, gelatin, albumin, collagen, dextran, or a dextran derivative. *See* De Ponti, page 5, ll. 6-9.

The term "heparin-binding growth factor" includes not only the natural human growth factor polypeptide, but also polypeptides that have biological activity similar to the natural human growth factor polypeptide. *See* De Ponti, page 4, ll. 5-14. The microspheres are generally loaded with an amount of growth factor effective to treat a wound or burn and can

be loaded with 0.2 to 5.0 mg of growth factor per gram of microspheres. *See* De Ponti, page 5, ll. 17-23. In addition, the powder may include microspheres that are not loaded with growth factor in order to dilute the powder. *See* De Ponti, page 5, ll. 24-25.

Further, on page 6, De Ponti discloses a process for preparing the powder, which comprises: (i) soaking water-insoluble and water-swellable polysaccharide microspheres in an aqueous solution of heparin-binding growth factor; and (ii) lyophilizing the dispersion of the microspheres in the aqueous growth factor solution. *See* De Ponti, page 6, ll. 19-24. The growth factor is loaded into the microspheres by first soaking a weighed amount of microspheres in a solution of the growth factor in water.

The ratio of microspheres to growth factor in solution can vary greatly. Several factors affect the degree of swelling of the microspheres, including the chemical composition of the microspheres, their unswollen diameter, the nature of their cross-linking agent and its relative content with reference to the microspheres, temperature, pH, ionic strength, nature of the solution and presence of surface modifiers. *See* De Ponti, page 8, ll. 4-10. De Ponti indicates that the microspheres are soaked for a sufficient time so that the growth factor is absorbed onto and/or into the microspheres and that the time can vary from 2 minutes to 48 hours. *See* De Ponti, page 8, ll. 10-14.

Following the soaking step, the microspheres are freeze-dried to remove the water. *See* De Ponti, page 8, ll. 16-17. Suitable results can be obtained from simple equipment to more complicated freeze driers. *See* De Ponti, page 8, ll. 18-25.

**III. The Examiner Has Not Established a *Prima Facie* Case of Obviousness**

As discussed above, in order to establish a *prima facie* case of obviousness, the Examiner must show that there is some suggestion or motivation, either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the references' teachings. In addition, the Examiner must show that there is a reasonable expectation of success. Finally, the Examiner must show that the prior art reference (or references when combined) teaches or suggests all the claim limitations.

De Ponti does not teach or suggest all of the limitations of the presently claimed invention and, moreover, the modification suggested by the Examiner would not have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. Further, De Ponti does not provide any motivation to modify the method disclosed in the reference, nor does it convey a reasonable expectation of success in making the claimed invention.

As admitted by the Examiner, De Ponti does not disclose or suggest a method of making a powdered pharmaceutical composition wherein primary loaded hydrogel particles are contacted with an aqueous composition containing the pharmacologically active agent for a period sufficient to allow further agent to associate with the hydrogel particles and be incorporated therewith as set forth in claim 64. Moreover, De Ponti does not disclose or suggest the steps of separating the hydrogel particles from the aqueous composition in at least a partial drying step to obtain "primary loaded hydrogel particles" having the active agent incorporated therewith or to obtain "secondary loaded hydrogel particles" having the active agent incorporated therewith.

In addition, De Ponti does not disclose or suggest the process where prior to the final drying step in part (f), the secondary loaded hydrogel particles formed through the partial drying step in part (e) are contacted at least one further time with an aqueous composition

containing said pharmacologically active agent for a period sufficient to allow still further agent to associate with the hydrogel particles and be incorporated therewith as set forth in claim 65. De Ponti also does not disclose or suggest providing a mixture of preformed particles. Finally, De Ponti does not disclose or suggest contacting the hydrogel particles with the aqueous composition while in a dry state according to claim 66 nor does it disclose contacting them while in a wet, prehydrated state according to claim 67. As such, De Ponti does not teach all of the limitations of the presently claimed invention.

De Ponti also does not disclose or suggest increasing the number of times that the microparticles are contacted with the growth factor solution and the number of times the particles are dried in at least a partial drying step to arrive at the claimed invention. To the contrary, De Ponti discloses varying the soaking time to achieve the desired amount of absorption onto and/or into the microspheres. *See* De Ponti, page 8, ll. 12-15. It also discloses other factors that affect the amount of swelling, including the chemical composition of the microspheres, their unswollen diameter, the nature of their cross-linking agent and its relative content with reference to the microspheres, temperature, pH, ionic strength, nature of the solution and presence of surface modifiers. *See* De Ponti, page 8, ll. 4-10. De Ponti does not suggest that one can affect the amount of swelling or the amount of growth factor absorbed onto and/or into the microsphere by increasing the number of times that the loaded hydrogel particles come into contact with an aqueous composition containing the pharmacologically active agent for a period sufficient to allow further agent to associate with the hydrogel particles and be incorporated therewith and by increasing the number of times the hydrogel particles are separated from the aqueous composition in at least a partial drying

step. Accordingly, De Ponti does not teach or suggest all of the limitations of the presently claimed invention.

The Examiner, however, takes the position that, absent unexpected results, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method disclosed in De Ponti by contacting the primary loaded hydrogel particles with an aqueous composition to allow further agent to associate with the hydrogel. The Examiner relies on the expectation of obtaining the desired swelling and amount of growth factor absorbed onto and / or into the microsphere as taught by De Ponti for the motivation to modify.

De Ponti, however, does not provide any motivation to modify the disclosed method that would render the claimed invention obvious under 35 USC § 103(a). As discussed above, De Ponti discloses several factors that affect the amount of swelling, including temperature, pH, ionic strength, etc., but does not disclose modifying the method by increasing the number of times that the microparticles are contacted with the growth factor solution and the number of times the particles are dried in at least a partial drying step to arrive at the claimed invention. *See* De Ponti, page 5, ll. 4-10. As a result, there is nothing in De Ponti that would have lead or suggested to a person of ordinary skill in the art to modify the teaching of De Ponti to arrive at the instantly claimed method.

In addition, the inventors of the present invention have discovered that, when the hydrogel particles are separated from the aqueous composition in at least a partial drying step to obtain primary loaded hydrogel particles and the primary loaded hydrogel particles are contacted with an aqueous composition containing the pharmacologically active agent for a further period, the amount of agent loaded can be more than double the original amount of

agent loaded on the hydrogel particles. This is illustrated in Example 5, and the results of two exemplary dual-loading processes are reported in Tables 1 and 2.

## CONCLUSION

De Ponti does not teach all of the limitations of the presently claimed invention and does not provide an objective motivation to modify the method disclosed in the reference. Accordingly, claims 64-71 and 81-87 are not obvious in light of De Ponti.

Respectfully submitted,

Date 23 June 2004

By _____ 40,413
for Richard C. Peet
Attorney for Applicant
Registration No. 35,792

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5483
Facsimile: (202) 672-5399

**Appendix A: Listing of the Claims on Appeal**

Claim 64. (Previously Presented): A method for making a powdered pharmaceutical composition, said method comprising:

(a) providing a mixture of pre-formed hydrogel particles;

(b) contacting the hydrogel particles with an aqueous composition containing at least one pharmacologically active agent for a period sufficient to allow the agent to associate with the hydrogel particles and be incorporated therewith;

(c) separating the hydrogel particles from the aqueous composition in at least a partial drying step to obtain primary loaded hydrogel particles having the active agent incorporated therewith;

(d) contacting the primary loaded hydrogel particles with an aqueous composition containing said pharmacologically active agent for a period sufficient to allow further agent to associate with the hydrogel particles and be incorporated therewith;

(e) separating the hydrogel particles formed in step (d) from the aqueous composition in at least a partial drying step to obtain secondary loaded hydrogel particles having the active agent incorporated therewith; and

(f) drying the secondary loaded hydrogel particles to obtain a powdered pharmaceutical composition.

Claim 65. (Previously Presented): The method of claim 64, wherein prior to step (f), the secondary loaded hydrogel particles formed in step (e) are contacted at least one further time with an aqueous composition containing said pharmacologically active agent for a period sufficient to allow still further agent to associate with the hydrogel particles and be incorporated therewith.

Claim 66. (Previously Presented): The method of claim 64, wherein the hydrogel particles in step (b) are contacted with the aqueous composition while in a dry state.

Claim 67. (Previously Presented): The method of claim 64, wherein the hydrogel particles in step (b) are contacted with the aqueous composition while in a wet, prehydrated state.

Claim 68. (Previously Presented): The method of claim 64, wherein the hydrogel particles comprise agarose, dextran, cellulose, chitin, starch, polyvinylpyrrolidone or polyvinyl alcohol.

Claim 69. (Previously Presented): The method of claim 64, wherein the active agent is present in the powdered pharmaceutical composition in an amount ranging from about 0.1 to 85 wt% of the composition.

Claim 70. (Previously Presented): The method of claim 64, wherein the powdered pharmaceutical composition is formed using a freeze-drying step.

Claim 71. (Previously Presented): The method of claim 64, wherein the powdered pharmaceutical composition is formed using a spray-drying step.

Claim 81. (Previously Presented): A method for making a powdered pharmaceutical composition, said method comprising:

(a) providing a mixture of pre-formed hydrogel particles;

(b) contacting the hydrogel particles with an aqueous composition containing at least one pharmacologically active agent for a period sufficient to allow the agent to associate with the hydrogel particles and be incorporated therewith;

(c) separating the hydrogel particles from the aqueous composition in at least a partial drying step to obtain primary loaded hydrogel particles having the active agent incorporated therewith;

(d) contacting the primary loaded hydrogel particles formed in step (c) at least one further time with an aqueous composition containing said pharmacologically active agent for a period sufficient to allow further agent to associate with the hydrogel particles and be incorporated therewith and separating the hydrogel particles formed from the aqueous composition at least one further time in at least a partial drying step to obtain loaded hydrogel particles having the active agent incorporated therewith; and

(e) drying the loaded hydrogel particles to obtain a powdered pharmaceutical composition.

Claim 82. (Previously Presented): The method of claim 81, wherein the hydrogel particles in step (b) are contacted with the aqueous composition while in a dry state.

Claim 83. (Previously Presented): The method of claim 81, wherein the hydrogel particles in step (b) are contacted with the aqueous composition while in a wet, prehydrated state.

Claim 84. (Previously Presented): The method of claim 81, wherein the hydrogel particles comprise agarose, dextran, cellulose, chitin, starch, polyvinylpyrrolidone or polyvinyl alcohol.

Claim 85. (Previously Presented): The method of claim 81, wherein the active agent is present in the powdered pharmaceutical composition in an amount ranging from about 0.1 to 85 wt% of the composition.

Claim 86. (Previously Presented): The method of claim 81, wherein the powdered pharmaceutical composition is formed using a freeze-drying step.

Claim 87. (Previously Presented): The method of claim 81, wherein the powdered pharmaceutical composition is formed using a spray-drying step.